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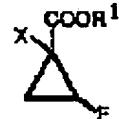
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(54) REDUCING DEHALOGENATION PROCESS

(57) Abstract:

PURPOSE: To obtain a fluorocyclopropane compound, especially a 1,2-cis-2-fluorocyclopropanecarboxylic acid derivative by reducing a 1-halogeno-2-fluoro-1-cyclopropane-carboxylic acid derivative.

CONSTITUTION: The fluorodichloropropanes of formula III can be produced by reducing a 1-halogeno-2-fluoro-1-cyclopropanecarboxylic acid derivative of formula I (X is Cl, Br or I; COOR¹ is ester group) with a compound of formula II [M is alkali or alkaline earth metal; R² is H, cyano, acyloxy or alkoxy; (m) is 1-4; (n) is 0-3; m+n is 4]. The reaction is preferably carried out in the presence of dimethyl sulfoxide, sulfolane, etc. The compound of formula III is useful as a production raw material for pharmaceuticals and agricultural chemicals. The cis-compound is preferentially produced by this process independent of the steric configuration of the starting raw material. The objective product is easily produced in high yield.



MBII, R²



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CLAIMS

[Claim(s)]

[Claim 1] Formula (I)

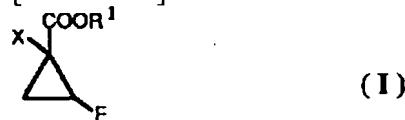
[Formula 1]



(X means a chlorine atom, a bromine atom, or an iodine atom among a formula.) COOR1 means ester. About the compound expressed, it is a formula (II).

[Formula 2] MBHmR2n (II) (M means an alkali-metal atom, an alkaline-earth-metal atom, or a zinc atom among a formula, and R2 means a hydrogen atom, a cyano group, an acyloxy radical, or the alkoxy group of carbon numbers 1-6.) m means the integer of 1 to 4, and n means the integer of 0 to 3, and the sum of m and n is 4. Process of the fluoro cyclopropanes characterized by processing with the compound expressed [claim 2] Formula (I)

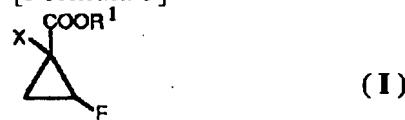
[Formula 3]



(X means a chlorine atom, a bromine atom, or an iodine atom among a formula.) COOR1 means ester. It is a formula (II) under existence of the compound more than a kind chosen from a sulfoxide compound and a sulfone compound in the compound expressed.

[Formula 4] MBHmR2n (II) (M means an alkali-metal atom, an alkaline-earth-metal atom, or a zinc atom among a formula, and R2 means a hydrogen atom, a cyano group, an acyloxy radical, or the alkoxy group of carbon numbers 1-6.) m means the integer of 1 to 4, and n means the integer of 0 to 3, and the sum of m and n is 4. Process of the fluoro cyclopropanes characterized by processing with the compound expressed [claim 3] The process according to claim 1 or 2 whose X of the compound of a formula (I) is a chlorine atom [claim 4] Formula (I)

[Formula 5]

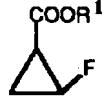


(X means a chlorine atom, a bromine atom, or an iodine atom among a formula.) COOR1 means ester. It is a formula (II) under existence of the compound more than a kind chosen from a sulfoxide compound and a sulfone compound in the compound expressed.

[Formula 6] MBHmR2n (II) (M means an alkali-metal atom, an alkaline-earth-metal atom, or a zinc

atom among a formula, and R2 means a hydrogen atom, a cyano group, an acyloxy radical, or the alkoxy group of carbon numbers 1-6.) m means the integer of 1 to 4, and n means the integer of 0 to 3, and the sum of m and n is 4. Formula characterized by processing with the compound expressed (III)

[Formula 7]



(III)

(-- COOR1 means ester among a formula.) -- process [claim 5] of a compound expressed The process according to claim 4 which consists of carrying out to the bottom of existence of a dialkyl sulfoxide [claim 6] The process according to claim 5 whose dialkyl sulfoxide is dimethyl sulfoxide [claim 7] The process according to claim 4 which consists of carrying out to the bottom of sulfolane existence [claim 8] The process according to claim 4, 5, 6, or 7 whose X of the compound of a formula (I) is a chlorine atom [claim 9] The process according to claim 8 whose compound of a formula (III) is a compound which has cis configuration

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DETAILED DESCRIPTION

[Detailed Description of the Invention]

[0001]

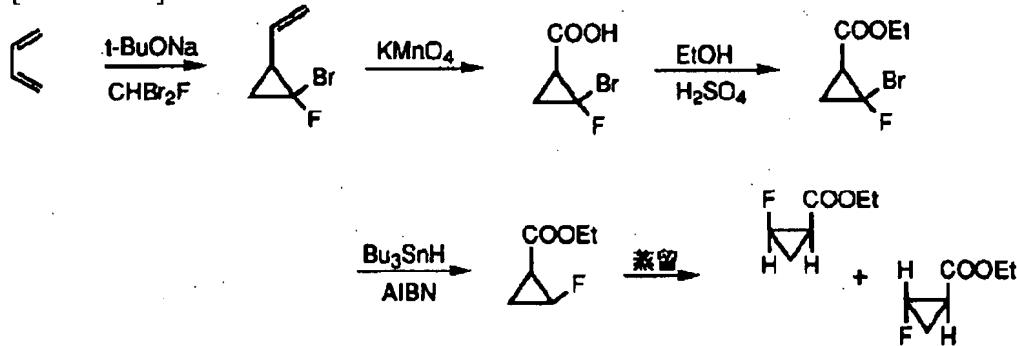
[Industrial Application] This invention relates to the process of fluoro cyclopropanes useful to manufacture of the compound which was excellent as physic and agricultural chemicals.

[0002]

[Description of the Prior Art] In the synthetic antibacterial drug of the new quinolone system which has the property which was excellent as a synthetic antibacterial drug, it is 1 and 2-cis- - 2 - The quinolone derivative which has a fluoro cyclo propyl group as a substituent of the 1st place combines strong antimicrobial activity and high safety, and is expected as an outstanding synthetic antibacterial drug (refer to JP,2-231475,A). This 1, 2-cis- - 2 - 1 [useful in order to build a fluoro cyclo propyl group], 2-cis- - 2 - This carboxylate for obtaining a fluoro cyclopropane carboxylic acid was compounded at the reaction of the four following processes which use a butadiene as a raw material (Wakayama University department-of-education bulletin 33 33 (1984)).

[0003]

[Formula 8]



[0004]

[Problem(s) to be Solved by the Invention] In the synthesis method of the conventional 2-fluoro cyclopropane carboxylic acid, there was a process which uses a trialkyltin hydride, for example, a tributyltin hydride, for the process. However, this trialkyltin hydride is difficult to use industrially in respect of toxicity or a price. Then, industrially applicable easy and simple development of the process of 2-fluoro cyclopropane carboxylic acid was desired.

[0005] this invention persons -- the result of wholeheartedly research -- 1-halogeno-2- Fluoro-1-processing a cyclopropane carboxylic-acid derivative on reduction conditions -- fluoro cyclopropanes, division, 1, and 2-cis--2- a fluoro cyclopropane carboxylic-acid derivative -- dominance -- and header this invention was completed for being obtained simple.

[0006]

[Elements of the Invention] This invention is a formula (I).

[Formula 9]



(X means a chlorine atom, a bromine atom, or an iodine atom among a formula.) COOR1 means ester. It is a formula (II) under existence of the compound more than a kind chosen from a sulfoxide compound and a sulfone compound in the compound expressed, or nonexistence.

[Formula 10] MBHmR2n (II) (M means an alkali-metal atom, an alkaline-earth-metal atom, or a zinc atom among a formula, and R2 means a hydrogen atom, a cyano group, an acyloxy radical, or the alkoxy group of carbon numbers 1-6.) m means the integer of 1 to 4, and n means the integer of 0 to 3, and the sum of m and n is 4. It is related with the process of the fluoro cyclopropanes characterized by processing with the compound expressed.

[0007] Furthermore, this invention is a formula (I).

[Formula 11]



(X means a chlorine atom, a bromine atom, or an iodine atom among a formula.) COOR1 means ester. It is a formula (II) under existence of the compound more than a kind chosen from a sulfoxide compound and a sulfone compound in the compound expressed.

[Formula 12] MBHmR2n (II) (M means an alkali-metal atom, an alkaline-earth-metal atom, or a zinc atom among a formula, and R2 means a hydrogen atom, a cyano group, an acyloxy radical, or the alkoxy group of carbon numbers 1-6.) m means the integer of 1 to 4, and n means the integer of 0 to 3, and the sum of m and n is 4. Formula characterized by processing with the compound expressed (III)

[Formula 13]



-- COOR1 means ester among a formula. -- it is related with the process of a compound expressed.

[0008] The compound (henceforth a compound (I)) of the formula (I) used in the approach of this invention is 1-halogeno. - It is 2. - It is a fluoro cyclopropane carboxylate derivative. Although it is good by the chlorine atom, the bromine atom, or the iodine atom as a halogen atom of the 1st place of this compound, it is a chlorine atom preferably.

[0009] Moreover, although COOR1 of a carboxylic-acid part should just be ester, as this ester, there may not be especially limitation and may be various ester. For example, they are alkyl ester, aryl ester, alkenyl ester, aralkyl ester, etc. As alkyl ester, they are methyl ester, ethyl ester, propyl ester, or butylester. Moreover, although phenyl ester is typical as aryl ester, a nitro group, an alkoxy group, an alkyl group, a cyano group, a halogen atom, or the amino group may permute this phenyl group further. Although benzyl is typical as aralkyl ester, it is easy to consist of about six alkylene groups from the aryl group and the carbon number 1. A nitro group, an alkoxy group, an alkyl group, a cyano group, a halogen atom, or the amino group may permute this aryl group further.

[0010] A compound (I) is compoundable by the approach of illustrating next. That is, if a dihalogeno acetic-ester compound and an acrylic ester compound are made to react to the bottom of base existence, the diester compound of the cyclopropane dicarboxylic acid which has the halogen atom 1 can be obtained. It enables it to cut the ester of the acrylic ester compound origin for the ester interchange radical of an acrylic ester compound alternatively here unlike the ester interchange radical of a dihalogeno acetic-ester compound. Using this selectivity, ester is cut and let one side of halogeno

dicarboxylic acid diester be the half ester compound of dicarboxylic acid. This compound is the half ester compound which the halogen atom has permuted by the carbon atom which carboxylate combines. If a molecule-like fluorine is made to react after changing this compound into a salt, fluorination will take place to a decarboxylation and coincidence and a compound (I) will be obtained.

[0011] Arrangement of the fluorine atom of the 2nd place of a compound (I) and the carboxylic-acid part of the 1st place has two sorts of what exists in a different side from what exists in the same field side of a cyclopropane ring (henceforth a cis- object in this specification) (henceforth a transformer object in this specification). In addition, the compound (it abbreviates to a compound (III) hereafter.) of a formula (III) is defined similarly.

[0012] By the approach of this invention, the compound (III) of a cis- object generates from the compound (I) of a cis- object. And it became clear that the compound (III) of a cis- object was obtained also from the compound (I) of a transformer object as a main product by the surprising thing.

[0013] the compound (III) generated when the compound (I) of a cis- object was processed by the approach of this invention -- setting -- the ratio of a cis- object and a transformer object -- about 10:0.5 it was . On the other hand, when the compound (I) of a transformer object was processed similarly, the direction of a cis- object generated many ratios of the cis- object in the generated compound (III), and a transformer object by about 10:1. Furthermore, the ratio of a cis- object and a transformer object When the compound (I) which is mixture with more 1.4:1 and cis- object was processed similarly, the ratio of the cis- object in the generated compound (III) and a transformer object was about 13:1. Thus, it became clear by using the approach of this invention that the compound (III) of a cis- object could be obtained in dominance.

[0014] 1-chloro -2 from which reduction of the carboxylate part instead of dehalogenation took place by the approach of this invention, and carboxylate became a hydroxymethyl group - Fluoro -1 - A hydroxymethyl propane (it may abbreviate to a hydroxymethyl object hereafter) is also generated. The direction in the case of processing the compound (I) of a transformer object generates more this hydroxymethyl object than the case where the compound (I) of a cis- object is processed. the case where the compound (I) of a transformer object is processed -- the generation rate of this by-product -- the compound (III) 10 of a cis- object -- receiving -- about -- Although it was 9.2, there was [as opposed to / by the case where the compound (I) of a cis- object is processed / the compound (III) 10 of a cis- object] nothing about 0.28. mixing ratio of a cis- object and a transformer object 1.4 -- the reaction from a compound with more cis- object (I) -- the compound (III) 13 of a cis- object -- receiving -- about -- There was nothing 0.2 (in addition, it asks for the generation ratio of various kinds of products described even here with a gas chromatography.). When a sulfoxide compound or a sulfone compound does not exist, this hydroxymethyl object's mainly generating is also clear.

[0015] Thus, if the approach of this invention is applied to the compound (I) of a transformer object, on the occasion of dehalogenation, a configuration will be reversed, and the compound (III) of a cis- object will generate (here, as for the essence of invention, it is unrelated whether reversal of the configuration of dehalogenation and a substituent advances gradually or it goes on instantaneous.). However, at the reaction using the compound (I) of a transformer object, it has also become clear that many hydroxymethyl objects generate as a by-product rather than the case of a cis- object. Since it is such, as a compound (I) for obtaining a compound (III), the cis- object is more more desirable. However, since the compound (III) of a cis- object generates in dominance according to the approach of this invention, about the coordination of the compound (I) of a raw material, it can be said that it is not necessary to mind so much.

[0016] Moreover, it became clear that the rate of a product changed also with the classes of ester in a compound (I). For example, the hydroxymethyl objects with which the direction of the ethyl ester of a compound (I) gives many cis- objects of a compound (III), and carries out a byproduction rather than methyl ester were few inclinations. Moreover, in the case of the third class butylester, generation of a hydroxymethyl object was not accepted.

[0017] The compounds (henceforth a compound (II)) of the formula (II) used by the approach of this invention are boron hydride metallic compounds. Although M means a metal atom, it is good here by an

alkaline-earth-metal atom or zinc atoms, such as alkali-metal atoms, such as a lithium, sodium, or a potassium, and calcium. Moreover, although R2 means a hydrogen atom, a cyano group, an alkoxy group, or an acyloxy radical, it is easy to be constituted as an alkoxy group here by the alkyl group of carbon numbers 1-6. As an acyloxy radical, an alkylcarbonyloxy radical, an aryl-carbonyloxy group, or aralkyl carbonyloxy group can be mentioned. They are still more specifically an acyloxy radical, a trifluoro acyloxy radical, a benzyloxy radical, benzyl carbonyloxy group, etc. Moreover, N-isobutyloxy carbonyl prolyl oxy-radical or N-benzyloxycarbonyl prolyl oxy-radical is sufficient.

[0018] What is necessary is just to usually use it as a compound (II), choosing from a sodium borohydride, a hydrogen boron lithium (lithium borohydride), boron hydride zinc (zinc borohydride), cyanidation boron sodium, hydrogenation alkoxy boron sodium, etc. It is easy to be the thing of carbon numbers 1-6 as an alkoxy group of hydrogenation alkoxy boron sodium. Among these, it is simplest to use a sodium borohydride.

[0019] When it is going to obtain a compound (III) by the approach of this invention, it is required to react to the bottom of existence of the compound more than a kind chosen from a sulfoxide compound and a sulfone compound. Here, you may choose and combine so that all may be chosen from a sulfoxide compound or a sulfone compound when making two or more sorts exist, and these both may be included. As a sulfoxide compound and a sulfone compound, dialkyl sulfoxides, annular sulfoxides, or annular sulfones can be mentioned, for example. Specifically, they are dimethyl sulfoxide, a sulfolane, etc. It is most common to use dimethyl sulfoxide as a compound chosen from a sulfoxide compound and a sulfone compound.

[0020] A phosphoric-acid amide compound can also be used for others, for example, hexamethylphosphoric triamide can be mentioned to them.

[0021] What is necessary is just to usually use about 3 time mol from 1, although what is necessary is just to use the amount of the compound (II) used in the 1 to 10 times as many range as this with the number of mols to a compound (I).

[0022] The approach of this invention mixes a compound (II) with a sulfoxide compound or a sulfone compound, and can carry it out by adding a compound (I) here. When it is going to obtain a compound (III) by the approach of this invention, especially a desirable thing is the approach of adding a compound (I) and going, after dissolving a compound (II) in a sulfoxide compound or a sulfone compound.

[0023] What is necessary is just to usually carry out in the range of 5 to 50 degrees C as reaction temperature. Moreover, it is good to carry out under cooling on the occasion of a reaction, when there is much calorific value.

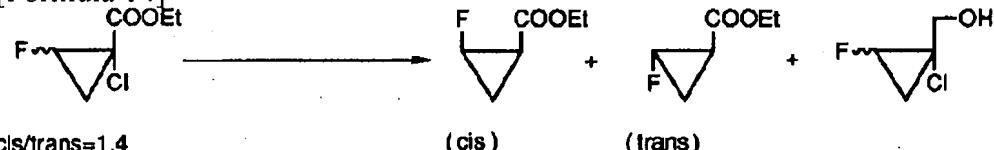
[0024] When it is going to obtain a compound (III) from a compound (I) using the approach of this invention, the yield of a compound (III) may improve by adding an additive to the system of reaction. As such an additive, acids, such as an inorganic acid, an organic acid, or Lewis acid, organic salt, mineral, etc. can be mentioned. As an organic acid, a boron-trifluoride ether complex can be mentioned as an acetic acid and Lewis acid. These should just apply the amount of catalysts in the system of reaction. On the other hand, a sodium fluoride (NaF), silver carbonate, or silver perchlorate can be mentioned as mineral. In the case of this sodium fluoride, it is the number of mols in the system of reaction. What is necessary is just to apply the amount of the range of equimolar from 0.1.

[0025]

[Example] Next, although an example is given and the approach of this invention is further explained to a detail, it cannot be overemphasized that this invention is not limited to this.

[0026] [Example 1] 1-chloro-2 in a sodium borohydride / dimethyl sulfoxide system - Dechlorination reaction of fluoro cyclopropane carboxylic-acid ethyl [0027]

[Formula 14]



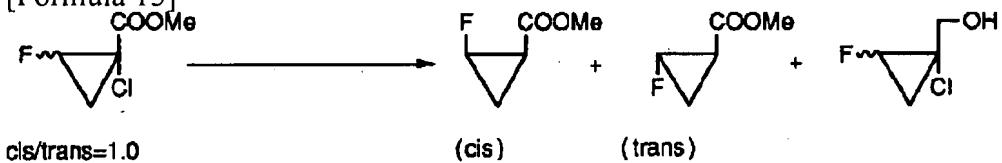
cis/trans=1.4

(cis) (trans)

[0028] 97% sodium borohydride It is dimethyl sulfoxide about 47 mg. 0.5 ml It dissolved and stirred under water cooling. It is 1-chloro to this solution. - 2 - Fluoro cyclopropane carboxylic-acid ethyl 167 mg After adding in 2 or 3 minutes, overnight stirring of the reaction mixture was carried out at the room temperature. The bottom of ice-cooling to reaction mixture, water 5 ml In addition, it considered as the homogeneity solution. It is the ether about this solution. It extracted in 10 ml and this extract was dried with sulfuric anhydride magnesium. The gas chromatography analyzed this solution. Consequently, reaction invert ratio The gas chromatography analysis ratio of a product was a cis- object:transformer object:hydroxymethyl object (2-chloro-1-fluoro-2- hydroxymethyl cyclopropane) =13:1:minute amount 100%.

[0029] [Example 2] 1-chloro -2 in a sodium borohydride / dimethyl sulfoxide system - Dechlorination reaction of fluoro cyclopropane carboxylic-acid methyl [0030]

[Formula 15]



[0031] 97% sodium borohydride It is dimethyl sulfoxide about 47 mg. 0.5 ml It dissolved and stirred under water cooling. It is 1-chloro to this solution. - 2 - Fluoro cyclopropane carboxylic-acid methyl 153 mg After adding in 2 or 3 minutes, overnight stirring of the reaction mixture was carried out at the room temperature. The bottom of ice-cooling to reaction mixture, water 5 ml In addition, it considered as the homogeneity solution. It is the ether about this solution. It extracted in 10 ml and the extract was dried with sulfuric anhydride magnesium. The gas chromatography analyzed this solution. consequently, reaction invert ratio the gas chromatography analysis ratio of 100% and a product -- cis-object:transformer object:hydroxymethyl object =10:1:2.9 it was .

[0032] [Example 3] 2-fluoro -1 - It is purity to eggplant mold KORUBEN of cyclopropane carboxylic-acid 200 ml. 97% of sodium borohydride 1.38 g It puts in and is bottom dimethyl sulfoxide of water cooling. 15 ml was added and it dissolved. 1-chloro -2 - After adding fluoro cyclopropane carboxylic-acid ethyl (a cis- object / transformer object = 1.4) and 4.9 g to the bottom of stirring in 10 minutes, cooling was stirred for two days at the stop room temperature. Reaction mixture is ice-cooled and it is water. After adding 40ml, it neutralized by concentrated hydrochloric acid. This solution was distilled and 2-fluoro cyclopropane carboxylic-acid ethyl distilled with water by boiling point 35-40 degree C/30 mmHg (water is included and it is 30 g.).

[0033] It is ethanol about the above-mentioned distillate. It dissolves in 30 ml and is under ice-cooling. Sodium-hydroxide water-solution 3 ml was dropped 50%. They are after dropping and reaction mixture at a room temperature 5.5 Time amount stirring was carried out and reduced pressure distilling off of the ethanol was carried out. It is ethyl acetate about the residue. It washed by 50 ml and the water layer was made into acidity by concentrated hydrochloric acid. It is ethyl acetate about this. It extracted 4 times in 60 ml, and the extract was dried with sulfuric anhydride magnesium. A solvent is distilled off. 2.14 g Cis- - 2 - The fluoro cyclopropane carboxylic acid was obtained as a colorless crystal. This thing 1 H-NMR The spectrum was in agreement with the preparation. Yield was 84% through two processes.

[0034] [Example 4] 2-fluoro -1 - It is purity to eggplant mold KORUBEN of cyclopropane carboxylic-acid 200 ml. 97% of sodium borohydride 3.07 g It puts in and is bottom dimethyl sulfoxide of water cooling. 30 ml was added and it dissolved. 1-chloro -2 - After adding fluoro cyclopropane carboxylic-acid methyl (a cis- object / transformer object = 1.4) and 10 g to the bottom of stirring in 30 minutes, cooling was stirred at the stop room temperature for 18 hours. Reaction mixture is ice-cooled and it is water. After adding 40ml, it neutralized by concentrated hydrochloric acid. This solution was distilled and 2-fluoro cyclopropane carboxylic-acid ethyl distilled with water by boiling point 32-35 degree C/35 mmHg (water is included and it is 45 g.).

[0035] The above-mentioned distillate is dissolved in a methanol and it is under ice-cooling. 50% sodium-hydroxide water solution 10 ml was dropped. Reaction mixture was stirred at the room temperature after dropping for 3 hours, and reduced pressure distilling off of the methanol was carried out. It is the ether about the residue. 100 ml It washed and the water layer was made into acidity by concentrated hydrochloric acid. It is ethyl acetate about this. 100 ml It extracted 4 times and the extract was dried with sulfuric anhydride magnesium. A solvent is distilled off. 4.97 g 2-fluoro cyclopropane carboxylic acid was obtained as a colorless crystal. This thing 1 H-NMR The ratio of a spectrum to a cis- object and a transformer object had the main cis- object at 10:1. Yield was 80% through two processes.

[0036] [Example 5] cis-1-chloro -2 in a sodium borohydride / dimethyl sulfoxide system - 97% sodium borohydride of dechlorination reactions of fluoro cyclopropane carboxylic-acid methyl It is dimethyl sulfoxide about 47 mg. 1 ml It dissolved and stirred under water cooling. It is cis-1-chloro to this solution. - 2 - Fluoro cyclopropane carboxylic-acid methyl 153 mg Dimethyl sulfoxide 1 ml The dissolved solution was dropped in 2 - 3 minutes. The following was processed like the example 1.

[0037] The gas chromatography analyzed the ether extract. Consequently, reaction invert ratio The gas chromatography analysis ratio of 100% and a product is cis- object:transformer object:hydroxymethyl object = 10:0.5. : It was 0.28.

[0038] [Example 6] trans-1-chloro -2 in a sodium borohydride / dimethyl sulfoxide system - It applies to the dechlorination reaction example 6 of fluoro cyclopropane carboxylic-acid methyl correspondingly, and is trans-1-chloro. - 2 - The dechlorination reaction was carried out using fluoro cyclopropane carboxylic-acid methyl.

[0039] The gas chromatography analyzed the ether extract. consequently, reaction invert ratio the gas chromatography analysis ratio of 100% and a product -- cis- object:transformer object:hydroxymethyl object = 10:1:9.8 it was .

[0040] [Example 7] 1-chloro -2 in a sodium borohydride / sulfolane system - 97% sodium borohydride of dechlorination reactions of fluoro cyclopropane carboxylic-acid ethyl It is a sulfolane about 47 mg. 1 ml It dissolved and stirred at the room temperature. It is 1-chloro to this solution. - 2 - Fluoro cyclopropane carboxylic-acid ethyl (a cis- object / transformer object = 1.4) and 167 mg Sulfolane 1 ml The dissolved solution was dropped in 2 - 3 minutes. Reaction mixture was stirred at the room temperature after dropping termination for 21 hours.

[0041] The bottom of ice-cooling to reaction mixture, water 10 ml is added and it is the ether. Reaction mixture was extracted in 10 ml and this extract was dried with sulfuric anhydride magnesium. The gas chromatography analyzed this solution. Consequently, for a reaction invert ratio, the gas chromatography analysis ratio of 50% and a product is cis- object:transformer object:hydroxymethyl object = 10. : It was 1.8:15.7.

[0042] [Example 8] 1-chloro -2 in a sodium borohydride / dimethyl sulfoxide system - 97% sodium borohydride of dechlorination reactions of fluoro cyclopropane carboxylic-acid tertiary butyl It is dimethyl sulfoxide about 97 mg. 1 ml It dissolved and stirred under water cooling. It is 1-chloro to this solution. - 2 - Fluoro cyclopropane carboxylic-acid tertiary butyl (a cis- object / transformer object = 1.5) 195 mg After adding in 2 - 3 minutes, reaction mixture was stirred at the room temperature for 22 hours. Water was added to reaction mixture, the ether extracted this, and this extract was dried with sulfuric anhydride magnesium. The gas chromatography analyzed this solution. Consequently, the gas-chromatography analysis ratio of a product of the reaction invert ratio was cis- object:transformer object = 13.5:1 46%. As for the hydroxymethyl object, generation was not accepted. On the other hand, the ratio of the cis- object in an unreacted substrate and a transformer object was cis- object:transformer object = 2.1:1. Therefore, it was guessed that the dechlorination reaction of the substrate of a transformer object is earlier compared with the dechlorination reaction of a cis- object.

[0043] 1-chloro -2 used at this reaction - Fluoro cyclopropane carboxylic-acid tertiary butyl is obtained as follows. 1-chloro -2 - Fluoro cyclopropane carboxylic-acid ethyl is processed in 1 convention sodium-hydroxide water solution in ethanol, and it hydrolyzes, and is 1-chloro. - 2 - It led to the fluoro cyclopropane carboxylic acid. Thus, after dissolving the obtained carboxylic acid in desiccation

dichloromethane and blowing isobutene into the bottom of ice-cooling under existence of the concentrated sulfuric acid of the amount of catalysts, it was made to agitate and react at a room temperature, and considered as the third class butylester.

[0044]

[Effect of the Invention] By using the approach of this invention, 2-fluoro cyclopropane carboxylic-acid derivative became possible [fluoro cyclopropanes and being obtained with simple and sufficient yield]. especially. and according to the approach of this invention, a fluorine atom and the compound which has a carboxylic-acid part in the same cyclopropane ring side (cis- object) boil the configuration of a raw material not related, generates it in dominance, and is excellent especially as a process of 2-fluoro cyclopropane carboxylic-acid derivative of a cis- object.

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TECHNICAL FIELD

[Industrial Application] This invention relates to the process of fluoro cyclopropanes useful to manufacture of the compound which was excellent as physic and agricultural chemicals.

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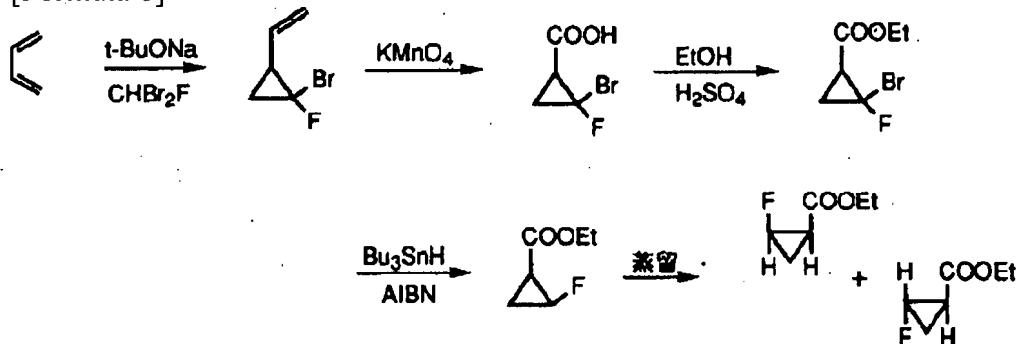
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PRIOR ART

[Description of the Prior Art] In the synthetic antibacterial drug of the new quinolone system which has the property which was excellent as a synthetic antibacterial drug, it is 1 and 2-cis- - 2 - The quinolone derivative which has a fluoro cyclo propyl group as a substituent of the 1st place combines strong antimicrobial activity and high safety, and is expected as an outstanding synthetic antibacterial drug (refer to JP,2-231475,A). This 1, 2-cis- - 2 - 1 [useful in order to build a fluoro cyclo propyl group], 2-cis- - 2 - This carboxylate for obtaining a fluoro cyclopropane carboxylic acid was compounded at the reaction of the four following processes which use a butadiene as a raw material (Wakayama University department-of-education bulletin 33 33 (1984)).

[0003]

[Formula 8]



[Translation done.]

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EFFECT OF THE INVENTION

[Effect of the Invention] By using the approach of this invention, 2-fluoro cyclopropane carboxylic-acid derivative became possible [fluoro cyclopropanes and being obtained with simple and sufficient yield] especially. and according to the approach of this invention, a fluorine atom and the compound which has a carboxylic-acid part in the same cyclopropane ring side (cis- object) boil the configuration of a raw material not related, generates it in dominance, and is excellent especially as a process of 2-fluoro cyclopropane carboxylic-acid derivative of a cis- object.

[Translation done.]

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TECHNICAL PROBLEM

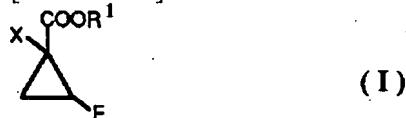
[Problem(s) to be Solved by the Invention] In the synthesis method of the conventional 2-fluoro cyclopropane carboxylic acid, there was a process which uses a trialkyltin hydride, for example, a tributyltin hydride, for the process. However, this trialkyltin hydride is difficult to use industrially in respect of toxicity or a price. Then, industrially applicable easy and simple development of the process of 2-fluoro cyclopropane carboxylic acid was desired.

[0005] this invention persons -- the result of wholeheartedly research -- 1-halogeno-2- Fluoro-1-processing a cyclopropane carboxylic-acid derivative on reduction conditions -- fluoro cyclopropanes, division, 1, and 2-cis--2- a fluoro cyclopropane carboxylic-acid derivative -- dominance -- and header this invention was completed for being obtained simple.

[0006]

[Elements of the Invention] This invention is a formula (I).

[Formula 9]

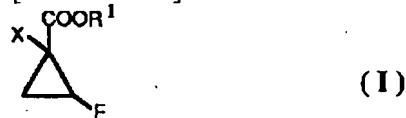


(X means a chlorine atom, a bromine atom, or an iodine atom among a formula.) COOR1 means ester. It is a formula (II) under existence of the compound more than a kind chosen from a sulfoxide compound and a sulfone compound in the compound expressed, or nonexistence.

[Formula 10] MBHmR2n (II) (M means an alkali-metal atom, an alkaline-earth-metal atom, or a zinc atom among a formula, and R2 means a hydrogen atom, a cyano group, an acyloxy radical, or the alkoxy group of carbon numbers 1-6.) m means the integer of 1 to 4, and n means the integer of 0 to 3, and the sum of m and n is 4. It is related with the process of the fluoro cyclopropanes characterized by processing with the compound expressed.

[0007] Furthermore, this invention is a formula (I).

[Formula 11]



(X means a chlorine atom, a bromine atom, or an iodine atom among a formula.) COOR1 means ester. It is a formula (II) under existence of the compound more than a kind chosen from a sulfoxide compound and a sulfone compound in the compound expressed.

[Formula 12] MBHmR2n (II) (M means an alkali-metal atom, an alkaline-earth-metal atom, or a zinc atom among a formula, and R2 means a hydrogen atom, a cyano group, an acyloxy radical, or the alkoxy group of carbon numbers 1-6.) m means the integer of 1 to 4, and n means the integer of 0 to 3, and the sum of m and n is 4. Formula characterized by processing with the compound expressed (III)

[Formula 13]



(-- COOR1 means ester among a formula.) -- it is related with the process of a compound expressed.

[0008] The compound (henceforth a compound (I)) of the formula (I) used in the approach of this invention is 1-halogeno. - It is 2. - It is a fluoro cyclopropane carboxylate derivative. Although it is good by the chlorine atom, the bromine atom, or the iodine atom as a halogen atom of the 1st place of this compound, it is a chlorine atom preferably.

[0009] Moreover, although COOR1 of a carboxylic-acid part should just be ester, as this ester, there may not be especially limitation and may be various ester. For example, they are alkyl ester, aryl ester, alkenyl ester, aralkyl ester, etc. As alkyl ester, they are methyl ester, ethyl ester, propyl ester, or butylester. Moreover, although phenyl ester is typical as aryl ester, a nitro group, an alkoxy group, an alkyl group, a cyano group, a halogen atom, or the amino group may permute this phenyl group further. Although benzyl is typical as aralkyl ester, it is easy to consist of about six alkylene groups from the aryl group and the carbon number 1. A nitro group, an alkoxy group, an alkyl group, a cyano group, a halogen atom, or the amino group may permute this aryl group further.

[0010] A compound (I) is compoundable by the approach of illustrating next. That is, if a dihalogeno acetic-ester compound and an acrylic ester compound are made to react to the bottom of base existence, the diester compound of the cyclopropane dicarboxylic acid which has the halogen atom 1 can be obtained. It enables it to cut the ester of the acrylic ester compound origin for the ester interchange radical of an acrylic ester compound alternatively here unlike the ester interchange radical of a dihalogeno acetic-ester compound. Using this selectivity, ester is cut and let one side of halogeno dicarboxylic acid diester be the half ester compound of dicarboxylic acid. This compound is the half ester compound which the halogen atom has permuted by the carbon atom which carboxylate combines. If a molecule-like fluorine is made to react after changing this compound into a salt, fluorination will take place to a decarboxylation and coincidence and a compound (I) will be obtained.

[0011] Arrangement of the fluorine atom of the 2nd place of a compound (I) and the carboxylic-acid part of the 1st place has two sorts of what exists in a different side from what exists in the same field side of a cyclopropane ring (henceforth a cis- object in this specification) (henceforth a transformer object in this specification). In addition, the compound (it abbreviates to a compound (III) hereafter.) of a formula (III) is defined similarly.

[0012] By the approach of this invention, the compound (III) of a cis- object generates from the compound (I) of a cis- object. And it became clear that the compound (III) of a cis- object was obtained also from the compound (I) of a transformer object as a main product by the surprising thing.

[0013] the compound (III) generated when the compound (I) of a cis- object was processed by the approach of this invention -- setting -- the ratio of a cis- object and a transformer object -- about 10:0.5 it was . On the other hand, when the compound (I) of a transformer object was processed similarly, the direction of a cis- object generated many ratios of the cis- object in the generated compound (III), and a transformer object by about 10:1. Furthermore, the ratio of a cis- object and a transformer object When the compound (I) which is mixture with more 1.4:1 and cis- object was processed similarly, the ratio of the cis- object in the generated compound (III) and a transformer object was about 13:1. Thus, it became clear by using the approach of this invention that the compound (III) of a cis- object could be obtained in dominance.

[0014] 1-chloro -2 from which reduction of the carboxylate part instead of dehalogenation took place by the approach of this invention, and carboxylate became a hydroxymethyl group - Fluoro -1 - A hydroxymethyl propane (it may abbreviate to a hydroxymethyl object hereafter) is also generated. The direction in the case of processing the compound (I) of a transformer object generates more this hydroxymethyl object than the case where the compound (I) of a cis- object is processed. the case where the compound (I) of a transformer object is processed -- the generation rate of this by-product -- the

compound (III) 10 of a cis- object -- receiving -- about -- Although it was 9.2, there was [as opposed to / by the case where the compound (I) of a cis- object is processed / the compound (III) 10 of a cis- object] nothing about 0.28. mixing ratio of a cis- object and a transformer object 1.4 -- the reaction from a compound with more cis- object (I) -- the compound (III) 13 of a cis- object -- receiving -- about -- There was nothing 0.2 (in addition, it asks for the generation ratio of various kinds of products described even here with a gas chromatography.). When a sulfoxide compound or a sulfone compound does not exist, this hydroxymethyl object's mainly generating is also clear.

[0015] Thus, if the approach of this invention is applied to the compound (I) of a transformer object, on the occasion of dehalogenation, a configuration will be reversed, and the compound (III) of a cis- object will generate (here, as for the essence of invention, it is unrelated whether reversal of the configuration of dehalogenation and a substituent advances gradually or it goes on instantaneous.). However, at the reaction using the compound (I) of a transformer object, it has also become clear that many hydroxymethyl objects generate as a by-product rather than the case of a cis- object. Since it is such, as a compound (I) for obtaining a compound (III), the cis- object is more more desirable. However, since the compound (III) of a cis- object generates in dominance according to the approach of this invention, about the coordination of the compound (I) of a raw material, it can be said that it is not necessary to mind so much.

[0016] Moreover, it became clear that the rate of a product changed also with the classes of ester in a compound (I). For example, the hydroxymethyl objects with which the direction of the ethyl ester of a compound (I) gives many cis- objects of a compound (III), and carries out a byproduction rather than methyl ester were few inclinations. Moreover, in the case of the third class butylester, generation of a hydroxymethyl object was not accepted.

[0017] The compounds (henceforth a compound (II)) of the formula (II) used by the approach of this invention are boron hydride metallic compounds. Although M means a metal atom, it is good here by an alkaline-earth-metal atom or zinc atoms, such as alkali-metal atoms, such as a lithium, sodium, or a potassium, and calcium. Moreover, although R2 means a hydrogen atom, a cyano group, an alkoxy group, or an acyloxy radical, it is easy to be constituted as an alkoxy group here by the alkyl group of carbon numbers 1-6. As an acyloxy radical, an alkylcarbonyloxy radical, an aryl-carbonyloxy group, or aralkyl carbonyloxy group can be mentioned. They are still more specifically an acyloxy radical, a trifluoro acyloxy radical, a benzyloxy radical, benzyl carbonyloxy group, etc. Moreover, N-isobutyloxy carbonyl prolyl oxy-radical or N-benzyloxycarbonyl prolyl oxy-radical is sufficient.

[0018] What is necessary is just to usually use it as a compound (II), choosing from a sodium borohydride, a hydrogen boron lithium (lithium borohydride), boron hydride zinc (zinc borohydride), cyanidation boron sodium, hydrogenation alkoxy boron sodium, etc. It is easy to be the thing of carbon numbers 1-6 as an alkoxy group of hydrogenation alkoxy boron sodium. Among these, it is simplest to use a sodium borohydride.

[0019] When it is going to obtain a compound (III) by the approach of this invention, it is required to react to the bottom of existence of the compound more than a kind chosen from a sulfoxide compound and a sulfone compound. Here, you may choose and combine so that all may be chosen from a sulfoxide compound or a sulfone compound when making two or more sorts exist, and these both may be included. As a sulfoxide compound and a sulfone compound, dialkyl sulfoxides, annular sulfoxides, or annular sulfones can be mentioned, for example. Specifically, they are dimethyl sulfoxide, a sulfolane, etc. It is most common to use dimethyl sulfoxide as a compound chosen from a sulfoxide compound and a sulfone compound.

[0020] A phosphoric-acid amide compound can also be used for others, for example, hexamethylphosphoric triamide can be mentioned to them.

[0021] What is necessary is just to usually use about 3 time mol from 1, although what is necessary is just to use the amount of the compound (II) used in the 1 to 10 times as many range as this with the number of mols to a compound (I).

[0022] The approach of this invention mixes a compound (II) with a sulfoxide compound or a sulfone compound, and can carry it out by adding a compound (I) here. When it is going to obtain a compound

(III) by the approach of this invention, especially a desirable thing is the approach of adding a compound (I) and going, after dissolving a compound (II) in a sulfoxide compound or a sulfone compound.

[0023] What is necessary is just to usually carry out in the range of 5 to 50 degrees C as reaction temperature. Moreover, it is good to carry out under cooling on the occasion of a reaction, when there is much calorific value.

[0024] When it is going to obtain a compound (III) from a compound (I) using the approach of this invention, the yield of a compound (III) may improve by adding an additive to the system of reaction.

As such an additive, acids, such as an inorganic acid, an organic acid, or Lewis acid, organic salt, mineral, etc. can be mentioned. As an organic acid, a boron-trifluoride ether complex can be mentioned as an acetic acid and Lewis acid. These should just apply the amount of catalysts in the system of reaction. On the other hand, a sodium fluoride (NaF), silver carbonate, or silver perchlorate can be mentioned as mineral. In the case of this sodium fluoride, it is the number of mols in the system of reaction. What is necessary is just to apply the amount of the range of equimolar from 0.1.

[Translation done.]

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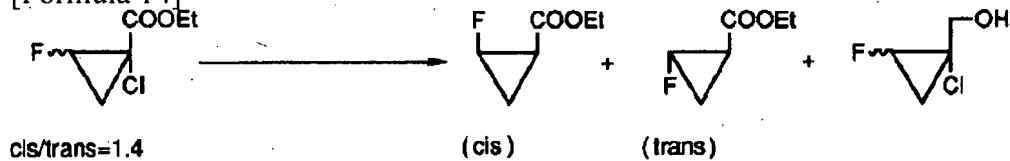
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EXAMPLE

[Example] Next, although an example is given and the approach of this invention is further explained to a detail, it cannot be overemphasized that this invention is not limited to this.

[0026] [Example 1] 1-chloro -2 in a sodium borohydride / dimethyl sulfoxide system - Dechlorination reaction of fluoro cyclopropane carboxylic-acid ethyl [0027]

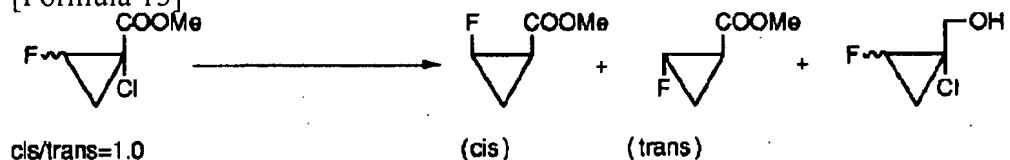
[Formula 14]



[0028] 97% sodium borohydride It is dimethyl sulfoxide about 47 mg. 0.5 ml It dissolved and stirred under water cooling. It is 1-chloro to this solution. - 2 - Fluoro cyclopropane carboxylic-acid ethyl 167 mg After adding in 2 or 3 minutes, overnight stirring of the reaction mixture was carried out at the room temperature. The bottom of ice-cooling to reaction mixture, water 5 ml In addition, it considered as the homogeneity solution. It is the ether about this solution. It extracted in 10 ml and this extract was dried with sulfuric anhydride magnesium. The gas chromatography analyzed this solution. Consequently, reaction invert ratio The gas chromatography analysis ratio of a product was a cis- object:transformer object:hydroxymethyl object (2-chloro-1-fluoro-2- hydroxymethyl cyclopropane) =13:1:minute amount 100%.

[0029] [Example 2] 1-chloro -2 in a sodium borohydride / dimethyl sulfoxide system - Dechlorination reaction of fluoro cyclopropane carboxylic-acid methyl [0030]

[Formula 15]



[0031] 97% sodium borohydride It is dimethyl sulfoxide about 47 mg. 0.5 ml It dissolved and stirred under water cooling. It is 1-chloro to this solution. - 2 - Fluoro cyclopropane carboxylic-acid methyl 153 mg After adding in 2 or 3 minutes, overnight stirring of the reaction mixture was carried out at the room temperature. The bottom of ice-cooling to reaction mixture, water 5 ml In addition, it considered as the homogeneity solution. It is the ether about this solution. It extracted in 10 ml and the extract was dried with sulfuric anhydride magnesium. The gas chromatography analyzed this solution. consequently, reaction invert ratio the gas chromatography analysis ratio of 100% and a product -- cis-object:transformer object:hydroxymethyl object =10:1:2.9 it was .

[0032] [Example 3] 2-fluoro -1 - It is purity to eggplant mold KORUBEN of cyclopropane carboxylic acid 200 ml. 97% of sodium borohydride 1.38 g It puts in and is bottom dimethyl sulfoxide of water cooling. 15 ml was added and it dissolved. 1-chloro -2 - After adding fluoro cyclopropane carboxylic

acid ethyl (a cis- object / transformer object = 1.4) and 4.9 g to the bottom of stirring in 10 minutes, cooling was stirred for two days at the stop room temperature. Reaction mixture is ice-cooled and it is water. After adding 40ml, it neutralized by concentrated hydrochloric acid. This solution was distilled and 2-fluoro cyclopropane carboxylic-acid ethyl distilled with water by boiling point 35-40 degree C/30 mmHg (water is included and it is 30 g.).

[0033] It is ethanol about the above-mentioned distillate. It dissolves in 30 ml and is under ice-cooling. Sodium-hydroxide water-solution 3 ml was dropped 50%. They are after dropping and reaction mixture at a room temperature 5.5 Time amount stirring was carried out and reduced pressure distilling off of the ethanol was carried out. It is ethyl acetate about the residue. It washed by 50 ml and the water layer was made into acidity by concentrated hydrochloric acid. It is ethyl acetate about this. It extracted 4 times in 60 ml, and the extract was dried with sulfuric anhydride magnesium. A solvent is distilled off. 2.14 g Cis- - 2 - The fluoro cyclopropane carboxylic acid was obtained as a colorless crystal. This thing 1 H-NMR The spectrum was in agreement with the preparation. Yield was 84% through two processes.

[0034] [Example 4] 2-fluoro -1 - It is purity to eggplant mold KORUBEN of cyclopropane carboxylic-acid 200 ml. 97% of sodium borohydride 3.07 g It puts in and is bottom dimethyl sulfoxide of water cooling. 30 ml was added and it dissolved. 1-chloro -2 - After adding fluoro cyclopropane carboxylic-acid methyl (a cis- object / transformer object = 1.4) and 10 g to the bottom of stirring in 30 minutes, cooling was stirred at the stop room temperature for 18 hours. Reaction mixture is ice-cooled and it is water. After adding 40ml, it neutralized by concentrated hydrochloric acid. This solution was distilled and 2-fluoro cyclopropane carboxylic-acid ethyl distilled with water by boiling point 32-35 degree C/35 mmHg (water is included and it is 45 g.).

[0035] The above-mentioned distillate is dissolved in a methanol and it is under ice-cooling. 50% sodium-hydroxide water solution 10 ml was dropped. Reaction mixture was stirred at the room temperature after dropping for 3 hours, and reduced pressure distilling off of the methanol was carried out. It is the ether about the residue. 100 ml It washed and the water layer was made into acidity by concentrated hydrochloric acid. It is ethyl acetate about this. 100 ml It extracted 4 times and the extract was dried with sulfuric anhydride magnesium. A solvent is distilled off. 4.97 g 2-fluoro cyclopropane carboxylic acid was obtained as a colorless crystal. This thing 1 H-NMR The ratio of a spectrum to a cis- object and a transformer object had the main cis- object at 10:1. Yield was 80% through two processes.

[0036] [Example 5] cis-1-chloro -2 in a sodium borohydride / dimethyl sulfoxide system - 97% sodium borohydride of dechlorination reactions of fluoro cyclopropane carboxylic-acid methyl It is dimethyl sulfoxide about 47 mg. 1 ml It dissolved and stirred under water cooling. It is cis-1-chloro to this solution. - 2 - Fluoro cyclopropane carboxylic-acid methyl 153 mg Dimethyl sulfoxide 1 ml The dissolved solution was dropped in 2 - 3 minutes. The following was processed like the example 1.

[0037] The gas chromatography analyzed the ether extract. Consequently, reaction invert ratio The gas chromatography analysis ratio of 100% and a product is cis- object:transformer object:hydroxymethyl object =10:0.5. : It was 0.28.

[0038] [Example 6] trans-1-chloro -2 in a sodium borohydride / dimethyl sulfoxide system - It applies to the dechlorination reaction example 6 of fluoro cyclopropane carboxylic-acid methyl correspondingly, and is trans-1-chloro. - 2 - The dechlorination reaction was carried out using fluoro cyclopropane carboxylic-acid methyl.

[0039] The gas chromatography analyzed the ether extract. consequently, reaction invert ratio the gas chromatography analysis ratio of 100% and a product -- cis- object:transformer object:hydroxymethyl object =10:1:9.8 it was .

[0040] [Example 7] 1-chloro -2 in a sodium borohydride / sulfolane system - 97% sodium borohydride of dechlorination reactions of fluoro cyclopropane carboxylic-acid ethyl It is a sulfolane about 47 mg. 1 ml It dissolved and stirred at the room temperature. It is 1-chloro to this solution. - 2 - Fluoro cyclopropane carboxylic-acid ethyl (a cis- object / transformer object = 1.4) and 167 mg Sulfolane 1 ml The dissolved solution was dropped in 2 - 3 minutes. Reaction mixture was stirred at the room temperature after dropping termination for 21 hours.

[0041] The bottom of ice-cooling to reaction mixture, water 10 ml is added and it is the ether. Reaction mixture was extracted in 10 ml and this extract was dried with sulfuric anhydride magnesium. The gas chromatography analyzed this solution. Consequently, for a reaction invert ratio, the gas chromatography analysis ratio of 50% and a product is cis- object:transformer object:hydroxymethyl object =10. : It was 1.8:15.7.

[0042] [Example 8] 1-chloro -2 in a sodium borohydride / dimethyl sulfoxide system - 97% sodium borohydride of dechlorination reactions of fluoro cyclopropane carboxylic-acid tertiary butyl It is dimethyl sulfoxide about 97 mg. 1 ml It dissolved and stirred under water cooling. It is 1-chloro to this solution. - 2 - Fluoro cyclopropane carboxylic-acid tertiary butyl (a cis- object / transformer object = 1.5) 195 mg After adding in 2 - 3 minutes, reaction mixture was stirred at the room temperature for 22 hours. Water was added to reaction mixture, the ether extracted this, and this extract was dried with sulfuric anhydride magnesium. The gas chromatography analyzed this solution. Consequently, the gas-chromatography analysis ratio of a product of the reaction invert ratio was cis- object:transformer object =13.5:1 46%. As for the hydroxymethyl object, generation was not accepted. On the other hand, the ratio of the cis- object in an unreacted substrate and a transformer object was cis- object:transformer object = 2.1:1. Therefore, it was guessed that the dechlorination reaction of the substrate of a transformer object is earlier compared with the dechlorination reaction of a cis- object.

[0043] 1-chloro -2 used at this reaction - Fluoro cyclopropane carboxylic-acid tertiary butyl is obtained as follows. 1-chloro -2 - Fluoro cyclopropane carboxylic-acid ethyl is processed in 1 convention sodium-hydroxide water solution in ethanol, and it hydrolyzes, and is 1-chloro. - 2 - It led to the fluoro cyclopropane carboxylic acid. Thus, after dissolving the obtained carboxylic acid in desiccation dichloromethane and blowing isobutene into the bottom of ice-cooling under existence of the concentrated sulfuric acid of the amount of catalysts, it was made to agitate and react at a room temperature, and considered as the third class butylester.

[Translation done.]

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CORRECTION OR AMENDMENT

[Kind of official gazette] Printing of amendment by the convention of 2 of Article 17 of Patent Law
[Section partition] The 2nd partition of the 3rd section
[Publication date] February 6, Heisei 13 (2001. 2.6)

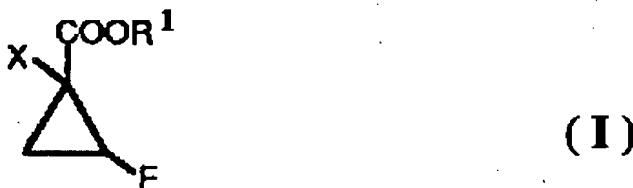
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[Procedure revision]
[Filing Date] May 12, Heisei 11 (1999. 5.12)
[Procedure amendment 1]
[Document to be Amended] Specification
[Item(s) to be Amended] Claim
[Method of Amendment] Modification
[Proposed Amendment]
[Claim(s)]
[Claim 1] Formula (I)
[Formula 1]



(X means a chlorine atom, a bromine atom, or an iodine atom among a formula.) COOR1 means ester. It is a formula (II) under existence of the compound more than a kind chosen from a sulfoxide compound

and a sulfone compound in the compound expressed.

[Formula 2] MBH_mR_{2n} (II)

(M means an alkali-metal atom, an alkaline-earth-metal atom, or a zinc atom among a formula, and R₂ means a hydrogen atom, a cyano group, an acyloxy radical, or the alkoxy group of carbon numbers 1-6.) m means the integer of 1 to 4, and n means the integer of 0 to 3, and the sum of m and n is 4.

Formula characterized by processing with the compound expressed (III)

[Formula 3]



(-- COOR¹ means ester among a formula.) -- process of a compound expressed

[Claim 2] The process according to claim 1 which consists of carrying out to the bottom of existence of a dialkyl sulfoxide

[Claim 3] The process according to claim 2 whose dialkyl sulfoxide is dimethyl sulfoxide

[Claim 4] The process according to claim 1 which consists of carrying out to the bottom of sulfolane existence

[Claim 5] The process according to claim 1, 2, 3, or 4 whose X of the compound of a formula (I) is a chlorine atom

[Claim 6] The process according to claim 5 whose compound of a formula (III) is a compound which has cis configuration

[Translation done.]